IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of: Farrar et al.

Title: Kappa Agonist Anti-Pruritic Pharmaceutical Formulations and Method of Treating Pruritus Therewith

Assistant Commissioner for Patents
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT PURSUANT TO 37 CFR 1.97 and 1.98

Dear Sir:

In accordance with the suggested procedure of 37 CFR 1.97 and 1.98, Applicants are submitting herewith copies of all of the prior art references identified on the enclosed list, which are considered to comprise the closest prior art of which the undersigned attorney, the inventors and anyone else believed to have been substantially involved in the preparation of this application are aware.

1. U.S. Patent No. 4,145,435, issued to Szmwszkovicz on March 20, 1979, discloses 2-aminocycloaliphatic amides as analgesics.

2. U. S. Patent No. 4,360,531, issued to McMillan et al on November 23, 1982, discloses substituted cycloalkanes as analgesics.

3. U. S. Patent No. 4,359,476, issued to Kaplan et al on November 16, 1982, discloses adjacently substituted cycloalkane-amide analgesics.

4. EPA 0 108 602, published May 16, 1984, discloses N-(2-aminocycloalkyl) benzamide and benzeneacetamide derivatives for the alleviation of pain.

5. U. S. Patent No. 4,855,316, issued to Horwell et al on August 8, 1989, discloses 1,2-diamino-4,5-dimethoxycyclohexyl amide analgesic compounds.

6. EPA 0 393 696, published October 24, 1990, discloses 7-(substituted)amino)-8-(substituted) carbonyl)-methylamino-1-oxaspiro(4,5)decanes as diuretics anti-inflammatory and cerebrovascular agents.

7. EPA 0 372 466, published June 13, 1990, discloses 2-amino-4 or 5-methoxycyclohexyl amides as analgesics.

8. U.S. Patent No. 4,906,655, issued to Horwell et al. on March 6, 1990, discloses 1,2-cyclohexylaminoaryl amides useful as analgesic agents.

9. U.S. Patent No. 4,438,130, issued to Kaplan on March 20, 1994, discloses analgesic 1-oxa, aza- and thia-spirocyclic compounds.

10. U.S. Patent No. 4,663,343, issued to Horwell et al on May 5, 1987, discloses substituted naphthalenyloxy-1,2,-diaminoxy-cyclohexyl amides as analgesics.

11. U. S. Patent No. 5,114,945, issued to Hayes et al on May 19, 1992, discloses spiropiperidine derivatives for the treatment of pain and cerebral ischemia.

12. U.S. Patent No. 4,943,578, issued to Naylor et al on July 24, 1990, discloses piperazine compounds for the treatment of pain and cerebral ischemia.

13. EPA 0 330 467, published August 30, 1989, discloses certain heterocyclic compounds for the treatment of pain and cerebral ischemia.

14. EPA 0 366 327, published May 2, 1990, discloses furo- and thieno[3,2-c]pyridines for the treatment of pain and cerebral ischemia.

15. EPA 0 398 720, published November 11, 1990, discloses piperazine derivatives for the treatment of pain.

16. EPA 0 330 469, published August 8, 1989, discloses tetrahydroisoquinoline derivatives as kappa agonists analgesics and for the treatment of cerebral ischemia.

17. WO 92/20657, published November 26, 1992, discloses 2-(pyrrolidinyl-1-methyl)-piperidine derivatives and their use as kappa agonists for the treatment of convulsions, cough,

asthma, inflammation, pancreatitis, arrhythmias, hyponatraemic disease states and cerebral ischemia.

18. EPA 0 409 489 A2, published January 23, 1991, discloses isoquinoline derivatives as analgesics.

19. EPA 0 333 427, published September 20, 1989, discloses certain heterocyclic derivatives for the treatment of pain.

20. WO 90/07502, published July 12, 1990, discloses decahydroisoquinoline compounds as analgesics.

21. EPA 0 356 247, published February 28, 1990 discloses analgesic carboxylic amide derivatives.

22. EP 0 752 246 A2 issued January 8, 1997, discloses certain kappa agonist compounds for use as analgesics.

23. WO 96/06077, published February 29, 1996, discloses N-[2-(pyrrolidinyl-1)-1phenylethyl]acetamides as kappa receptor agonist useful as analgesics, anti-inflammatory, diuretic and neuroprotective agents.

24. EP 0 483 580, A2, issued October 14, 1991, discloses 1-(2-arylethyl)-pyrrrolidines as analgesics.

25. EPA 0 254 545, published January 27, 1988, discloses diamine compounds useful as analgesics.

26. EPA 0 325 406, published July 26, 1989, discloses diamine compounds useful for the treatment of hypertension and inflammation.

27. EPA 0 261 842, published March 30, 1988, discloses N-1-acylated-(1-phenyl or benzyl)-1,2-ethylene diamines useful in the treatment of pain.

28. WO 96/06077, published February 29, 1996, discloses N-[2-(pyrrolidinyl-1)-1-phenylethyl]acetamides as kappa receptor antagonists useful as analgesics, anti-inflammatories, diuretics and neuroprotective agents.

29. WO 94/18165, published August 18, 1994, discloses sulfonamide compounds as kappa-receptor agonists for the treatment of pain, asthma, scabies, psoriasis and inflammation.

30. WO 96/06078, published February 29, 1996, discloses N-(2-(pyrrolidinyl-1)-1-phenylethyl) acetamide as kappa receptor antagonists useful as analgesic, anti-inflammatory, diuretic and neuroprotective agents.

31. EPA 0 577 847 A1, published January 12, 1994, discloses morphinan derivatives as analgesic and diuretic agents.

32. U.S. Patent No. 4,929,627, issued to Pannev on May 29, 1990, discloses benzo-fused cycloalkane and oxa- and thia- cycloalkane trans-1,2-diamine derivatives as analgesics and diuretics.

33. EPA 0 260 555, published March 23, 1988, discloses benzo-fused cycloalkane and oxa- and thia- cycloalkane tans-1,2-diamine derivatives as analgesics and diuretics.

34. IL Farmaco, 50(6), 405-418 (1995) discloses central and peripheral analgesic agents.

35. McMahon et al., TINS, Vol. 15, No. 12, 1992, relates to "Itching for an explanation" describing the characteristics of itching and comparing them to the characteristics of pain.

36. Bernstein et al. in the Journal of Investigative Dermatology, 78:82-83, 1982, describe a study in which pre-treatment of normal subjects with naloxone hydrochloride resulted in diminution or abolition of histamine-provoked itch.

37. Ballantyne et al., in Pain, 33:149-160, 1988, describe, in a review article, that itching occurs as a side effect when opiates are administered by the epidural and spinal routes. The itching is treatable with naloxone.

38 J. D. Bernhard in J. Am. Acad. Derm., 24:309, 1991, described basic and clinical aspects of itch.

39. IASP Newsletter, Sept/Oct 1996 describes the neuronal mechanisms of itch sensation. The description starts with the quote from a German physician of more than three centuries ago that: "Itch is an unpleasant sensation which evokes the desire to scratch". The newsletter cites experiments of others who found that peripherally applied opioids have analgesic action in peripheral tissue but aggravate histamine itch.

40. Thomas et al. in "Microinjection of morphine into the rat medullary dorsal horn produces a dose-dependent increase in facial scratching", Brain Research, 695:267-270, 1995, report a study involving injection of morphine into rats which resulted in a scratching response. Scratching was attenuated by the injection of naloxone.

References 1-34 disclose compounds useful as analgesics, diuretics, anti-inflammatories and neuroprotective agents. None recognizes that the compounds can be used for the prevention or treatment of pruritus.

None of the above-cited references disclose or suggest the present invention as claimed.

Respectfully submitted,

Date: October 4/99

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